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10/591,612	07/16/2007	Teruo Okano	GRT/159-102	3397

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EXAMINER	
WILSON, MICHAEL C	
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1632	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,612	OKANO ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-41* is/are pending in the application.

4a) Of the above claim(s) *25 and 40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-24,26-39 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7-12-10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-21 have been canceled. Claims 27-41 have been added. Claims 22-41 are pending.

Election/Restrictions

Claim 25 remains and new claim 40 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the non-human animal does not have to be prepared using the method of claims 22 or 27. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 25 and 40 have been withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 22-24, 26-39 and 41 are under consideration.

Applicant's arguments filed 12-27-10 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicants are reminded that they must provide support for each new phrase and claim in an amendment. Support for each new phrase and claim should be provided in the opening paragraphs of each response by applicant. Failure to do so may result in a new matter rejection if support is not readily apparent. Applicants should provide

support for each phrase and claim using page and line numbers of the specification as originally filed.

Because claims 1 and 27 share significant similarity, it would have been better to merely amend claim 1 for ease of prosecution and examination.

Claim Objections

Claim 27 is objected to because it should use steps a)-d) as in claim 22. The "cultivating" step in claim 27 should be clarified, i.e. –cultivating the cancer cells on the support at a temperature at which the polymer has a weak hydration force--. The "adjusting" step in claim 27 should be another "cultivating" step, i.e. –cultivating the cancer cells on the support at a temperature at which the polymer has a strong hydration force--.

Claim Rejections - 35 USC § 112

New Matter

Claims 22-24, 26-39 and 41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection of claim 1 regarding the phrase "polymer having a lower critical temperature for dissolution" has been withdrawn because the claim has been canceled.

The rejection of claims 14 and 16 regarding the phrase "which has a tumor formed from the sheet of cancer cells, and evaluating the effect of the administered test

substance based on increase or decrease in the volume and/or weight of the tumor" has been withdrawn because the claims have been canceled.

Claim 22 as amended is new matter. Support for the phrase "but the cell culture support is not a mixture of a polymer and collagen" has not been provided and none can be found in the specification as originally filed.

Claim 22 as amended is new matter. Support for the phrase "without being treated with a proteolytic enzyme or ethylene glycol bis)2-aminoethylether) tetraacetic acid (EGTA)" has not been provided and none can be found in the specification as originally filed.

Claim 27 is new matter. Support has not been provided for the claims and is not readily apparent from the specification as originally filed. In particular, support for the phrases "the hydration force of which changes in a temperature range of…", "in a temperature region where", "weak hydration force", "stronger hydration force" and "on which transplantation is to be performed" cannot be found in claim 27.

Claims 28-39 and 41 are new matter. Support has not been provided for the claims and is not readily apparent from the specification as originally filed.

Applicants are reminded that they must provide for each new phrase in an amendment and for each phrase in a new claim in an amendment. Support for each new phrase in each new claim should be provided in the opening paragraphs of each response. Applicants should cite the page and line numbers of the original specification when providing support for new phrases and claims.

Enablement

Claims 22-24 and 26 remain and claims 27-39 and 41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making a non-human animal having transplanted cancer cells comprising i) preparing a cell culture support coated with poly N-isopropylacrylamide, ii) cultivating cancer cells on the cell culture support at a temperature in which the cells adhere and grow, iii) decreasing the temperature so that the cancer cells detach from the support, and iv) transplanting the detached cancer cells to a non-human animal, does not reasonably provide enablement for any polymer that changes its hydration force as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 22 is drawn to a process for preparing a cancer cell-transplanted non-human animal comprising:

(a) preparing a cell culture support coated on a surface, wherein the cell culture support is comprised of a polymer which shifts from a dehydrated state to a hydrated state in the temperature range of 0-80℃ but the cell culture support is not a mixture of a polymer and collagen, wherein the polymer is obtained by polymerization of one or more monomers selected from the group consisting of (meth)acrylamide compounds, N-(or N,N-di)alkyl-substituted (meth)acrylamide derivatives, and vinyl ether derivatives;

(b) cultivating cancer ceils on the cell culture support at a temperature at which the polymer is dehydrated;

(c) cooling the cell culture support to a temperature at which the polymer is hydrated, whereby a sheet of cancer cells is detached from the cell culture support without being treated with a proteolytic enzyme or ethylene glycol bis(2-aminoethylether) tetraacetic acid (EGTA); and

(d) transplanting the sheet of cancer cells to a specified site of a non-human animal.

Claim 27 is drawn to a process for preparing a cancer cell-transplanted non-human animal comprising the steps of preparing a cell culture support coated on a surface with a polymer the hydration force of which changes in a temperature range of 0-80 ℃, wherein the cell culture support is not a mixture of a polymer and collagen, then cultivating cancer cells on the support in a temperature region where the polymer has weak hydration force, thereafter adjusting the culture solution to a temperature at which the polymer has a stronger hydration force, whereby the cultured cancer cells are detached from the cell culture support without being treated with a proteolytic enzyme or ethylene glycol bis(2-aminoethylether) tetraacetic acid (EGTA), and transplanting the detached cancer cells to a specified site of a non-human animal on which transplantation is to be performed.

The specification states JP 05/192138 taught a method of

> "skin cells cultivation comprising the steps of preparing a cell culture support which has a surface of its base coated with a polymer having an upper or lower critical temperature for dissolution in water in a range of 0-80℃, cultivating skin cells on the cell culture support at a temperature not higher than the upper critical temperature for dissolution or at a temperature not lower than the lower critical temperature for dissolution, and thereafter adjusting the temperature to above the upper critical temperature for dissolution or below the lower critical temperature for dissolution, whereby the cultured skin cells are detached. This

method depends on temperature adjustment for detaching the cells from the culture base coated with the temperature-responsive polymer."

Example 1 describes a:

"cell culture base was coated with the temperature- responsive polymer poly(N-isopropylacrylamide) in an amount of 2.0 μg/cm2 and the cancer cells NCI-H460 was cultivated (2 x 104 cells were seeded; 37℃ in 5% C02). Three days later, the cancer cells (NCI-H460) on the culture base were confirmed to have become confluent; thereafter, a cultured cell moving jig comprising a polyacrylic plate coated with a fibrin gel was gently placed over the cultured cell sheet so that the cultured cancer cells adhered to it; then, the cell culture base was cooled at 20℃ for 60 minutes. After the cooling, the detached cell sheet was collected from the jig together with the fibrin gel and a piece of the gel with the adhering cell sheet (7 mm x 17 mm x 2 mm; 5 x 10^5 cells) was transplanted subcutaneously to the back of each of 10 nude mice" (pg 13).

Paragraph 16, pg 7-8, teaches the polymer can be obtained by homo- or copolymerization of monomers selected from the group consisting of monomers include (meth)acrylamide compounds, N- (or N,N- di)alkyl-substituted (meth)acrylamide derivatives, and vinyl ether derivatives.

Rejections

A. The specification and the art do not provide adequate guidance that any polymer obtained by homo- or co-polymerization of one or more monomers as broadly claimed would detach in a sheet without being treated with a proteolytic enzyme or EGTA as broadly claimed other than poly(N-isopropylacrylamide). It would have required those of skill undue experimentation to determine other polymers that would detach in a sheet as claimed because not all of such compounds would work. Therefore, the claims should be limited to using poly(N-isopropylacrylamide).

Response to arguments

Applicants argue the specification taught polymers other than poly(N-isopropylacrylamide). Applicants' argument is not persuasive. The specification does not provide adequate guidance that any other polymer obtained by homo- or copolymerization of monomers selected from the group consisting of monomers include (meth)acrylamide compounds, N- (or N,N- di)alkyl-substituted (meth)acrylamide derivatives, and vinyl ether derivatives would detach in a sheet as claimed. If the polymers on pg 7-8 are capable of detaching cells in a sheet as claimed, then the specific conditions required to detach cells in a sheet are wholly unclear. Applicants do not correlate the poly(N-isopropylacrylamide) polymer to the polymers on pg 7-8 such that those of skill could reasonably expect they change hydration force from 0-80˚ and detach cells in a sheet as claimed. Applicants do not teach the conditions required to detach cells in a sheet using any polymer as broadly claimed.

B. Claims 22 and 27 encompass transplanting any species of cancer cells into any species of non-human animal. The claims encompass transplanting any species of non-human cancer cells into the same species of non-human animal. The specification suggests making a nude mouse, rat, mouse, guinea pig, and rabbit and exemplifies making a nude mouse. The specification states any species of cancer cells can be used (pg 6, paragraph 14, line 10-12). However, for the animal to be a model of human cancer, it must comprise human cancer cells. For the animal to support the growth of human cancer cells, it must not reject the cells. The only means described for maintaining human cancer cells in an animal model is if the animal is

immunocompromised, and the only immunocompromised animal described by applicants is a nude mouse. If the animal is not immunocompromised, the cancer cells will be attacked by the host's immune system, be destroyed and fail to create a tumor. The specification does not teach how to use an animal that rejects the cancer cells. The specification does not teach how to use a non-human animal having cancer cells from the same species as a model of human cancer. Overall, the claims encompass too numerous combinations of cancer cells/non-human animals of different species that would not work to be considered "non-operative embodiments", and applicants do not provide adequate guidance to use a non-human animal with cancer cells of the same species as a model of human cancer. Therefore, the claims should be limited to using human cancer cells in a nude mouse.

Response to arguments

Applicants argue cancer cells of one species can be transplanted into a non-human animal of the same species. Applicants' argument is not persuasive. First, the claims encompass an inordinate number of combinations of one species of cancer cells and a different species of non-human animal. At minimum, applicants should amend the claims to exclude the exponential number of non-operative embodiments. Second, applicants do not teach how to use a non-human animal with cancer cells from the same species as a model of human cancer. Therefore, the claims should be limited using human cancer cells in a nude mouse.

C. Claim 26 is drawn to a method of selecting agents that treat tumors by administering a test substance to an animal before and/or after transplanting cancer cells. The claim is dependent upon the method of claim 22; however, the claim is unclear (see 112/2nd). For this rejection, it is assumed the claims are directed to a method of using animals made by the method of claim 22. The claim is not enabled because the specification does not provide adequate guidance how to perform the method by teaching the specific steps of administering agents, the controls or how to compare the results so that agents that treat cancer are identified. Without such guidance, applicants have left those of skill with undue experimentation to determine the steps for using animals made by the method of claim 22 to identify agents that treat cancer. Clarification is required.

Response to arguments

Applicants argue the steps required to select agents that treat tumors using the non-human animals made by the method of claims 1, 3 and 22 would be known to the skilled artisan. Applicants' argument is not persuasive because it is unfounded. The steps in claims 14 and 16 are not disclosed in the specification as originally filed and are not readily apparent (see New Matter rejection). If the animal and methods of using the animal are known in the art, then why are applicants claiming the animal (claims 13 and 15) and methods of using the animals (claims 14, 16 and 26). If the animal and methods of using the animal are novel, how can the techniques required to use the animal be “conventional?” Overall, the disclosure fails to explicitly or implicitly teach the

specific steps of administering agents, the controls or how to compare the results so that agents that treat cancer are identified.

Indefiniteness

Claims 22-24 and 26 remain and claims 27-39 and 41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The temperature "region wherein the polymer has weak hydration force" in claim 27 is indefinite. The metes and bounds of when a hydration force is "weak" are not defined in the specification or art at the time of filing. The specification does not teach how to determine when a polymer is in a temperature range that causes a weak hydration force. Without such guidance, those of skill would not be able to determine when they were infringing on the claim.

Likewise, the temperature "at which the polymer has a stronger hydration force" in claim 27 is indefinite. The metes and bounds of when a hydration force is "stronger" are not defined in the specification or art at the time of filing. The specification does not teach how to determine when a polymer is in a temperature range that causes a stronger hydration force. Without such guidance, those of skill would not be able to determine when they were infringing on the claim.

The phrases "the cancer cells sheet" and "the cancer tissue in the non-human animal" in claim 29 lack antecedent basis. Furthermore, it remains unclear what

applicants are attempting to limit about the size and shape of the detached cancer cells sheet. Accordingly, it cannot be determined how the phrase further limits claim 27

Claim 31 is indefinite because the metes and bounds of when a cancer cell is from a “transplantable” cell line. Accordingly, the claim does not further limit the structure or function of the cell line.

Claim 33 is indefinite because the metes and bounds of when a cancer cell is from an “untransplantable” cell line. Accordingly, the claim does not further limit the structure or function of the cell line.

The metes and bounds of claim 35 are indefinite because all living cells are collected from living tissue.

The phrase “the polymer the hydration force of which changes in a temperature range of 0-80℃ is" in claim 38 does not makes sense.

Claim 41 is indefinite because it never clearly set forth administering an agent to an animal made by the process of claim 27.

Claim Rejections - 35 USC § 102

The rejection of claims 1, 3, 5-7, 9, 12, 13 under 35 U.S.C. 102(b) as being anticipated by Koezuka (Nippon Nogei Kagaku Kaishi, 1994, Vol. 68, No. 4, pg 783-792, abstract only) has been withdrawn because the claims have been canceled.

Claims 27-31, 33, 35, 37-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Koezuka (Nippon Nogei Kagaku Kaishi, 1994, Vol. 68, No. 4, pg 783-792, abstract only) in view of applicants’ arguments.

This rejection assumes Koezuka taught a poly(N-isopropylacrylamide) polymer as argued by applicants in the response filed 6-26-09, pg 12, and the conditions required to detach cells in a sheet.

Koezuka taught culturing human cancer cells from a primary culture on a thermoresponsive poly(N-isopropylacrylamide) polymer, detaching the cells from the polymer without trypsin and transplanting the cells to nude mice. The conditions described by Koezuka inherently detach cells in a sheet as claimed because the cells are on poly N-isopropylacrylamide polymer and because the conditions are described by applicants as being part of the invention. The claims do not exclude using dextran sulfate or EGTA. Claims 31 and 33 are included because the primary culture described by Koezuka is either a transplantable or untransplantable cell line.

Applicants' arguments are noted but do not address the basis of the rejection as it relates to claims 27-31, 33, 35, 37-39. In particular, Applicants argue Koezuka differs from the claimed invention because Koezuka taught collagen, dextran sulfate and EGTA treatment were indispensable conditions. Applicants' argument is not persuasive. The claims use open language and encompass using collagen, dextran sulfate and EGTA treatment. Furthermore, it is not readily apparent from the specification that applicants contemplated excluding collagen, dextran sulfate or EGTA. Specifically, pg 12, line 2, contemplates using collagen.

Claim Rejections - 35 USC § 103

The rejection of claims 1, 3, 5-13, 15, 16, 21 under 35 U.S.C. 103(a) as being unpatentable over Koezuka (Nippon Nogei Kagaku Kaishi, 1994, Vol. 68, No. 4, pg 783-

792, abstract only) in view of Sakai (JP 05/192138) has been withdrawn because the claims have been canceled.

The rejection of claims 22-24 and 26 under 35 U.S.C. 103(a) as being unpatentable over Koezuka (Nippon Nogei Kagaku Kaishi, 1994, Vol. 68, No. 4, pg 783-792, abstract only) in view of Sakai (JP 05/192138) has been withdrawn because the combined teachings of Koezuka and Sakai did not teach "but the cell culture support is not a mixture of a polymer and collagen" as in claim 22 as amended.

Claims 22-24, 27-31, 33, 35, 37-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koezuka (Nippon Nogei Kagaku Kaishi, 1994, Vol. 68, No. 4, pg 783-792, abstract only) in view of Sakai (JP 05/192138).

Koezuka taught culturing human cancer cells from a primary culture on a thermoresponsive N-isopropylacrylamide polymer, detaching the cells from the polymer without trypsin and transplanting the cells to nude mice (see anticipation rejection above). This rejection assumes Koezuka did not teach the specific conditions required to detach cells using poly(N-isopropylacrylamide) polymer as in claims 22 and 27. The abstract of Koezuka did not teach performing the method in the absence of collagen and without EGTA as in claim 22 as newly amended.

However, methods of culturing cells with poly (N-isopropylacrylamide) were known in the art as described by Sakai. The specification acknowledges that JP 05/192138 taught a method of

> "skin cells cultivation comprising the steps of preparing a cell culture support which has a surface of its base coated with a polymer having an upper or

> lower critical temperature for dissolution in water in a range of 0-80℃, cultivating skin cells on the cell culture support at a temperature not higher than the upper critical temperature for dissolution or at a temperature not lower than the lower critical temperature for dissolution, and thereafter adjusting the temperature to above the upper critical temperature for dissolution or below the lower critical temperature for dissolution, whereby the cultured skin cells are detached. This method depends on temperature adjustment for detaching the cells from the culture base coated with the temperature-responsive polymer."

Thus, the specific conditions required to detach cells in a sheet using poly(N-isopropylacrylamide) were known as supported by Sakai.

Thus, it would have been obvious to those of ordinary skill in the art at the time the invention was made to culture cancer cells on poly(N-isopropylacrylamide), detach the cancer cells from the primary culture using EGTA, and transplant the cells into nude mice as taught by Koezuka using the conditions for detaching cells from poly(N-isopropylacrylamide) in a sheet described by Sakai. Those of ordinary skill in the art would have been motivated to use the conditions for detaching cells in a sheet described by Sakai for ease of manipulation and to prevent leakage of the cells from the site of transplantation. Since the cells are attached to each other in a sheet, they would be less likely to leak from the site of transplantation.

The translation of Sakai shows Sakai taught performing the method in the absence of collagen and without EGTA (see Examples in Sakai) as in claim 22. Thus, it would have been obvious to those of ordinary skill in the art at the time the invention was made to culture cancer cells on poly(N-isopropylacrylamide), detach the cancer cells from the primary culture, and transplant the cells into nude mice as taught by Koezuka in the absence of collagen or without EGTA as described by Sakai. Those of ordinary skill in the art would have been motivated to remove collagen to save money

and time. Those of ordinary skill in the art would have been motivated to replace EGTA with any other compound known in the art at the time of filing that would detach cells in a sheet as the compounds were interchangeable. It was well within the purview of those of ordinary skill to choose any of a number of compounds capable of detaching cells in a sheet at the time of filing.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

Response to arguments

Applicants argue Koezuka differs from the claimed invention because Koezuka taught collagen, dextran sulfate and EGTA treatment were indispensable conditions. Applicants' argument is not persuasive. The claims use open language and encompass using collagen, dextran sulfate and EGTA treatment. Furthermore, it is not readily apparent from the specification that applicants contemplated excluding collagen, dextran sulfate or EGTA. Specifically, pg 12, line 2, contemplates using collagen.

Applicants argue Sakai applied the method to skin cells and not to cancer cells as claimed. Applicants' argument is not persuasive. The type of cells in the sheet formed is irrelevant. Sakai has been relied upon to indicate that those of ordinary skill would have readily known the conditions required to detach cancer cells from poly(N-isopropylacrylamide) as described by Koezuka.

Applicants' arguments regarding cancer cell-transplanted animals themselves are noted but are irrelevant. The claims are drawn to methods of making cancer cell-transplanted animals, and all the method steps claimed were known at the time of filing.

Applicants' arguments regarding improving known cancer-cell animal models are noted but are irrelevant. The claims are not "improvement" claims. Furthermore, the method of Koezuka produced an animal having such an improvement, and Sakai merely taught the conditions required to detach cancer cells from poly(N-isopropylacrylamide). If applicants believe the conditions required to detach cancer cells from poly(N-isopropylacrylamide) are different than those of Sakai, i.e. changing the temperature ("This method depends on temperature adjustment for detaching the cells from the culture base coated with the temperature-responsive polymer"), clarification is required.

Claims 22-24, 27-31, 33, 35, 37-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koezuka (Nippon Nogei Kagaku Kaishi, 1994, Vol. 68, No. 4, pg 783-792, abstract only) in view of Sakai (JP 05/192138) and Hirose (Biomacromolecules, 2000, Vol. 1, pg 377-381).

The combined teachings of Koezuka and Sakai taught culturing human cancer cells from a primary culture on a thermoresponsive N-isopropylacrylamide polymer, detaching the cells from the polymer without trypsin and transplanting the cells to nude mice (see obviousness rejection above). This rejection assumes the combined teachings of Koezuka and Sakai did not teach performing the method in the absence of collagen and without EGTA as in claim 22 as amended.

However, methods of culturing cells with poly (N-isopropylacrylamide) in the absence of collagen to obtain a sheet of cells were known in the art as described by

Hirose. The sheets were detached without any need of an enzyme such as trypsin (abstract), so the EDTA of Koezuka can be replaced with the method of Hirose, which is equivalent to the phrase "without being treated with a proteolytic enzyme or ethylene glycol bis(2-aminoethylether) tetraacetic acid (EGTA)" as in claim 22.

Thus, it would have been obvious to those of ordinary skill in the art at the time the invention was made to culture cancer cells on poly(N-isopropylacrylamide), detach the cancer cells from the primary culture using EGTA, and transplant the cells into nude mice as taught by the combined teachings of Koezuka and Sakai in the absence of collagen described by Hirose. Those of ordinary skill in the art would have been motivated to perform the method without collagen to save money and time.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday through Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

/Michael C. Wilson/
Primary Patent Examiner